



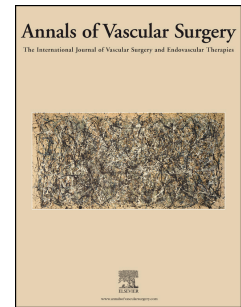
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COVID-19 Related Peripheral Arterial Thrombosis Treated in a Large Health Managed Organization

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## Abstract

Objectives: COVID-19 was initially identified as an acute respiratory disease but it was quickly recognized that multiple organ systems could be affected. Complications of venous thrombosis and pulmonary embolism have been well reported. However, there is a paucity of data on COVID-19 related arterial thrombosis. The aim of this study was to examine the incidence, characteristics, treatment and outcome in patients with acute COVID-19 related arterial thrombosis in a large health maintenance organization (HMO).

Methods: A retrospective multi-center case review was performed from March 2020 to March 2021. Cases were identified through a questionnaire sent to vascular surgeons at each of the HMO associated hospitals. Patient characteristics, imaging, treatment and outcome were reviewed. Successful revascularization was defined as restoration of blood flow with viability of the end organ and absence of death within 30 days. Limb salvage was defined as prevention of major amputation (transtibial or transfemoral) and absence of death in 30 days.

Results: There were 37,845 patients admitted to our associated hospitals with COVID-19 complications during this time. Among this group, 26 patients (0.07%) had COVID-19 related arterial thrombosis. The mean age was 61.7 years (range 33-82 years) with 20 men (77%) and 6 women (23%). Ethnic minorities comprised 25/26 of cases (96%). Peripheral arterial disease (PAD) was present in 4/26 (15%), active smoking in 1/26 (3.8%), and diabetes in 19/26 (73%). Most patients developed acute arterial ischemia in the outpatient setting, 20/26 (77%). Of the outpatients, 6/20 (30%) had asymptomatic COVID-19 and 14/20 (70%) had only mild upper respiratory symptoms. Distribution of ischemia was as follows: 23 patients had at least one lower extremity ischemia, one patient had cerebral and lower extremity, one had mesenteric and lower extremity, and one had upper extremity ischemia. Revascularization was attempted in 21

patients, of which 12/21 (57%) were successful. Limb salvage was successful in 13/26 (50%). Overall mortality was 31% (8/26).

Conclusions: Our experience in a large HMO revealed that the incidence of COVID-19 related arterial thrombosis was low. The actual incidence is likely to be higher since our method of case collection was incomplete. The majority of arterial thrombosis occurred in the outpatient setting in patients with either asymptomatic or mild/moderate COVID-19 respiratory disease. Acute ischemia was the inciting factor for hospitalization in these cases. Acute lower extremity ischemia was the most common presentation and limb salvage rate was lower than that expected when compared to ischemia related to PAD. Arterial thrombosis associated with COVID-19 portends a significantly higher mortality. Education of primary care providers is paramount to prevent delayed diagnosis as most patients initially developed ischemia in the outpatient setting and did not have a high cardiovascular risk profile.

## Introduction

COVID-19 was initially recognized in Wuhan, China in December 2019 and by January 2020 the first cases in the United States were reported. By March 2020, COVID-19 was declared a pandemic primarily recognized to cause acute respiratory distress. However, it became apparent that COVID-19 impacted multiple organ systems. In particular, complications of unprovoked venous thrombosis were noted. This has been postulated to be due to a severe inflammatory response that incites a generalized hypercoagulable state.<sup>1</sup> The earliest studies on COVID-19 coagulopathy suggested that an increase in the vasoconstrictive Angiotensin II as well as a decrease in the vasodilator angiotensin, and the release of cytokines secondary to sepsis combined to trigger a hypercoagulable state.<sup>2</sup> Others have postulated that increased autoimmune antibodies may incite an inflammatory state predisposing to thrombosis.<sup>3</sup> Venous thrombosis has

been extensively reported while COVID-19 related arterial thrombosis has been less well described. We report our case series of 26 patients presenting with COVID-19 related arterial thrombosis.

## **Material and Methods**

A retrospective multi-center case review was performed for patients with acute COVID-19 associated arterial thrombosis treated at Southern California Kaiser Permanente hospitals from March 2020 thru March 2021. Patients were identified through survey responses that were sent to vascular surgeons at each of the eleven health plan hospitals. Internal review board approval was obtained. Chart review was done using an electronic health system to identify patient characteristics, imaging, treatment and outcomes. Characteristics including age, ethnicity, smoking status, history of coronary or peripheral artery disease, and statin, steroid, and anticoagulant usage were recorded. The type of arterial ischemia was detailed along with the onset of ischemia in relation to onset of COVID-19 symptoms, Rutherford classification, and inpatient versus outpatient presentation. Treatment was examined in terms of type of intervention, limb salvage, length of hospital stay and mortality. Successful revascularization was defined as restoration of blood flow with viability of the end organ and absence of death within 30 days. Limb salvage was defined as prevention of major amputation (transtibial or transfemoral) and absence of death in 30 days. Age was compared using a t-test and all other variables with chi-square test.

## **Results**

From March 2020 to March 2021, 37,845 patients were admitted with diagnosis of COVID-19 across our eleven health plan hospitals. Twenty-six patients with COVID-19 related arterial

thrombosis were identified through survey responses constituting an incidence of 0.07%. Patient demographics are detailed in Table 1. Mean age was 61.7 years with age ranging from 33 to 82 and the majority of patients were of ethnic minority 96% (25/26). Latinos were the largest minority group at 73% (19/26). Smoking history was present in only 38.4% (10/26) with only one active smoker 3.8%. Hyperlipidemia was present in 80.8% (21/26), obesity in 38.4% (10/26), and both coronary artery disease and peripheral artery disease in 15.4% (4/26), respectively. There were 5 patients (19.2%) already on anticoagulation primarily for atrial fibrillation. Four patients were taking antiplatelet medications (15.4%) and 18 were on statins (69.2%). Of the combined factors of active smoking, obesity, diabetes, CAD, hypertension, hyperlipidemia, A fib, and CKD, only 1 (3.8%) patient had zero factors, 3 (11.5%) had combined 1 factor, 5 (19.2%) had combined 2 factors, and 17 (65.4%) had 3 or more factors.

Patient presentation at time of ischemia, Rutherford classification, and distribution of ischemia are displayed in Table 2. Most patients presented from the outpatient setting at 77% (20/26). Exclusively lower extremity ischemia was most common and occurred in 88.5% of cases (23/26).

Treatment for acute ischemia included anticoagulation only in 15.4% (4/26), surgical thrombectomy/bypass in 50% (13/26), and endovascular thrombectomy/thrombolysis in 7.7% (2/26) of patients (Table 3). One patient underwent primary amputation while 28.6% (6/21) of patients required a secondary amputation after failed surgical or endovascular thrombectomy. Ultimately, the successful revascularization and limb salvage rate was relatively low at 50% (13/26) and mortality was high at 30.8% (8/26).

Mortality was examined in relation to demographics (Table 4). Obesity was considered a positive indicator of survival with a P value of 0.0072. Atrial fibrillation was associated with increased



risk of death. Diabetes, hypertension, and hyperlipidemia all had a higher percent mortality but did not reach statistical significance. Mortality did not seem to correlate with Rutherford classification (Table 5). The mean number of morbidities did not differ significantly among those who survived versus died (Table 6).

Amputation outcomes were analyzed against each demographic factor and comorbidity (Table 7). Age was associated with an inverse relationship to likelihood of amputation. Both obesity and hypertension had a significantly increased risk of amputation. Diabetics had a higher amputation rate but this did not reach statistical significance.

## **Discussion**

The actual incidence of COVID-19 related arterial thrombosis is difficult to calculate but appeared to be low in our HMO during the COVID-19 pandemic of 2020-2021. The reported value only captures severe cases requiring Vascular Surgery intervention and likely underestimates the true incidence given it was based on a voluntary query of providers. In addition, it could be argued that the relationship with acute ischemia and COVID-19 could be incidental in some of our patients.

We found that the majority of patients affected with COVID-19 arterial thrombosis were ethnic minorities, which highlights the disparity of COVID adverse outcomes on race. Arterial thrombosis occurred across the age spectrum and did not spare the younger age groups, as would typically ischemia caused by atherosclerosis. Indes et al had comparable findings in which COVID-19 positive patients with arterial thromboembolic complications were younger compared to those that developed similar complications but were COVID-19 negative.<sup>4</sup>

The most salient feature was that the onset of acute arterial ischemia did not seem related to the severity of COVID-19 respiratory disease. The majority of our patients had only mild COVID-19 symptoms and developed acute ischemia while at home. Similar findings were reported by Wengerter et al, in which limb-threatening large vessel arterial thrombosis was not found to be associated with the severity of pulmonary infection.<sup>5</sup> This is in contrast to COVID-19 associated venous thromboembolism in which there has been reported correlation between severity of COVID-19 illness and requirements for higher level of care.<sup>6</sup>

Our patient cohort did not have high cardiovascular atherosclerotic risk factors. This finding is supported by other reports showing lack of correlation with COVID arterial thromboembolic events in large vessel distributions and underlying atherosclerosis risks.<sup>4,7</sup>

We found that younger age was associated with a higher risk of limb amputation. We postulate that this could be due to a delay in diagnosis, as clinicians may tend to misdiagnose ischemic symptoms in this younger age group without classical atherosclerotic risk factors. Our low limb salvage rate has been noted in other studies as well, presumed to be due to the virus-related hypercoagulable state<sup>8</sup>. The mortality rate was also higher in this cohort than the overall COVID-19 mortality rate in the United States. A study from Jordan had similar findings in which there was an increased mortality rate in patients with COVID-19 pneumonia who developed acute limb ischemia relative to their general COVID-19 mortality rate.<sup>9</sup>

Our findings are limited in statistical significance due to the small sample size. However, it is unlikely any large series of COVID-19 associated arterial thrombosis will be reported given its relatively low incidence. Therefore, smaller descriptive reports like ours will be helpful to understand the overall disease process.

## Conclusion

Our experience in a large HMO revealed that the incidence of severe COVID-19 related arterial thromboembolic events requiring in patient hospitalization and Vascular Specialist consultation was low. The majority of arterial thrombosis occurred in the outpatient setting in patients with either asymptomatic or mild/moderate COVID-19 respiratory disease. Acute ischemia was the inciting factor for hospitalization in these cases. Acute lower extremity ischemia was the most common presentation and limb salvage rate was lower than that expected for ischemia related to PAD. Arterial thrombosis associated with COVID-19 portends a significantly higher mortality. Education of primary care providers is paramount to prevent delayed diagnosis as most patients initially developed ischemia in the outpatient setting, were of younger age, and did not have a classical cardiovascular high risk profile.

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Table 1: Demographics and Associated Comorbidities

Age mean (range)	61.7 mean (range 33-82)
Ethnicity	(19 )73.1% Latino, (3) 11.5% Asian, (2) 7.7% Black, (1) 3.8% Middle Eastern, (1) 3.8% White
Smoking	(15) 57.7% Non-smoker, (10) 38.5% Quit, (1) 3.8% Active
Obesity	(10) 38.4%
Diabetes Mellitus	(19) 73.1%
Coronary Artery Disease	(4) 15.4%
Hypertension	(16) 61.5%
Hyperlipidemia	(21) 80.8%
Atrial Fibrillation	(8) 30.8%
Chronic Kidney Disease/ End Stage Renal Disease	(3) 11.5%
Peripheral Artery Disease	(4) 15.4%
Statin use	(18) 69.2%
Pre-Covid Anticoagulation	(5) 19.2%

Table 2: Presentation

Outpatient	(20) 76.9%
Inpatient	(6) 23.1%
Ischemia Distribution: Lower extremity	(23) 88.5%
Ischemia Distribution: Upper extremity	(1) 3.8%
Ischemia Distribution: Mesenteric and lower extremity	(1) 3.8%
Ischemia Distribution: Cerebral and lower extremity	(1) 3.8%
Rutherford Class I	(5) 19.2%
Rutherford Class IIA	(7) 26.9%
Rutherford Class IIB	(7) 26.9%
Rutherford Class 3	(7) 26.9%

Table 3: Interventions and Outcomes

Anticoagulation	(4) 15.4%
Surgical thrombectomy/bypass	(13) 50%
Endovascular thrombectomy/thrombolysis	(2) 7.7%
Primary Amputation	(1) 3.8%
Secondary amputation after failed intervention	(6) 23.1%
Successful revascularization/Limb Salvage rate	(13) 50%
Mortality	(8) 30.8%

Table 4: Mortality Based on Demographics and Comorbidities

	Alive	Dead	Total	p-value
Age				0.1258
N	18	8	26	
Mean (SD)	59.4 (12.42)	66.8 (10.63)	61.7 (12.18)	
Median	61.5	66.0	62.0	
Q1, Q3	54.0, 65.0	62.0, 74.5	56.0, 69.0	
Range	(33.0-83.0)	(47.0-82.0)	(33.0-83.0)	
Ethnicity				0.2332
Arab	1 (5.6%)	0 (0%)	1 (3.8%)	
Asian	1 (5.6%)	2 (25%)	3 (11.5%)	
Black	2 (11.1%)	0 (0%)	2 (7.7%)	
Caucasian	0 (0%)	1 (12.5%)	1 (3.8%)	
Latino	14 (77.8%)	5 (62.5%)	19 (73.1%)	
Smoking				0.6179
N	11 (61.1%)	4 (50%)	15 (57.7%)	
Q	6 (33.3%)	4 (50%)	10 (38.5%)	
Y	1 (5.6%)	0 (0%)	1 (3.8%)	
Obesity				<b>0.0072</b>
N	8 (44.4%)	8 (100%)	16 (61.5%)	
Y	10 (55.6%)	0 (0%)	10 (38.5%)	
Diabetes Mellitus				0.4176
N	4 (22.2%)	3 (37.5%)	7 (26.9%)	
Y	14 (77.8%)	5 (62.5%)	19 (73.1%)	
Coronary artery				0.7858



disease				
N	15 (83.3%)	7 (87.5%)	22 (84.6%)	
Y	3 (16.7%)	1 (12.5%)	4 (15.4%)	
Hypertension				0.3469
N	8 (44.4%)	2 (25%)	10 (38.5%)	
Y	10 (55.6%)	6 (75%)	16 (61.5%)	
Hyperlipidemia				0.6188
N	3 (16.7%)	2 (25%)	5 (19.2%)	
Y	15 (83.3%)	6 (75%)	21 (80.8%)	
Atrial Fibrillation				<b>0.0194</b>
N	15 (83.3%)	3 (37.5%)	18 (69.2%)	
Y	3 (16.7%)	5 (62.5%)	8 (30.8%)	
CKD/ESRD				0.9185
N	16 (88.9%)	7 (87.5%)	23 (88.5%)	
Y	2 (11.1%)	1 (12.5%)	3 (11.5%)	

Table 5: Mortality Based on Rutherford Classification

Rutherford Class	Alive	Dead	Total	P-value
1	5 (27.8%)	1 (12.5%)	6 (23.1%)	0.6874
2	7 (38.9%)	4 (50%)	11 (42.3%)	
3	6 (33.3%)	3 (37.5%)	9 (34.6%)	

Table 6: Mean Number Morbidities Related to Mortality

	Alive	Dead	Total	p-value
Num_factors				0.8642
N	18	8	26	
Mean (SD)	3.2 (1.83)	3.0 (1.60)	3.2 (1.74)	
Median	3.5	3.5	3.5	
Q1, Q3	2.0, 4.0	2.0, 4.0	2.0, 4.0	
Range	(0.0-6.0)	(0.0-5.0)	(0.0-6.0)	

Table 7: Amputation Based on Demographics and Comorbidities

	No amputation	Amputation	Total	p-value
Age				<b>0.0345</b>
N	19	7	26	
Mean (SD)	63.6 (13.43)	<b>56.6 (5.94)</b>	61.7 (12.18)	
Median	65.0	57.0	62.0	
Q1, Q3	60.0, 74.0	52.0, 62.0	56.0, 69.0	
Range	(33.0-83.0)	(46.0-62.0)	(33.0-83.0)	
Ethnicity				0.0413
Arab	1 (5.3%)	0 (0%)	1 (3.8%)	
Asian	3 (15.8%)	0 (0%)	3 (11.5%)	
Black	0 (0%)	2 (28.6%)	2 (7.7%)	
Caucasian	0 (0%)	1 (14.3%)	1 (3.8%)	
Latino	15 (78.9%)	4 (57.1%)	19 (73.1%)	
Smoking				0.8118
N	11 (57.9%)	4 (57.1%)	15 (57.7%)	
Q	7 (36.8%)	3 (42.9%)	10 (38.5%)	
Y	1 (5.3%)	0 (0%)	1 (3.8%)	
Obesity				<b>0.0360</b>
N	14 (73.7%)	2 (28.6%)	16 (61.5%)	
Y	5 (26.3%)	<b>5 (71.4%)</b>	10 (38.5%)	
Diabetes Mellitus				0.0603
N	7 (36.8%)	0 (0%)	7 (26.9%)	
Y	12 (63.2%)	7 (100%)	19 (73.1%)	

Coronary artery disease				0.9249
N	16 (84.2%)	6 (85.7%)	22 (84.6%)	
Y	3 (15.8%)	1 (14.3%)	4 (15.4%)	
Hypertension				<b>0.0144</b>
N	10 (52.6%)	0 (0%)	10 (38.5%)	
Y	9 (47.4%)	7 (100%)	16 (61.5%)	
Hyperlipidemia				0.6978
N	4 (21.1%)	1 (14.3%)	5 (19.2%)	
Y	15 (78.9%)	6 (85.7%)	21 (80.8%)	
Atrial Fibrillation				0.2690
N	12 (63.2%)	6 (85.7%)	18 (69.2%)	
Y	7 (36.8%)	1 (14.3%)	8 (30.8%)	
CKD/ESRD				0.7901
N	17 (89.5%)	6 (85.7%)	23 (88.5%)	
Y	2 (10.5%)	1 (14.3%)	3 (11.5%)	
Rutherford Class				0.3409
1	5 (26.3%)	1 (14.3%)	6 (23.1%)	
2	9 (47.4%)	2 (28.6%)	11 (42.3%)	
3	5 (26.3%)	4 (57.1%)	9 (34.6%)	